CLINICAL PHARMACOLOGY REVIEW

Date: August 25, 2000 (final)

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Subject: Clinical Pharmacology Review of BLA 99-1488 (PEG-Intron)

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Please see attached review.

Clinical Pharmacology Review of BLA 99-1488

PK Studies Summary:

1. **Protocol I95-010: Rising, single-dose safety and tolerability of PEG-IFN α-2b in healthy volunteers**

Methods

This was a Phase 1, randomized, open-label, active-controlled (Intron A), rising SQ single-dose, 6 parallel-arm study conducted in 60 healthy male and female adults (n= 10/group; 8 PEG-IFN: 2 Intron A). Dose groups:

Group	PEG-IFN Dose (ug/kg)	OR	Intron A Dose (MIU)
1	0.07 x 1 dose		3 q 48 hr x 3 doses
2	0.14 x 1 dose		3 q 48 hr x 3 doses
3	0.35 x 1 dose		3 q 48 hr x 3 doses
4	0.7 x 1 dose		1 x 1 dose
5	0.5 x 1 dose		1 x 1 dose
6	0.035 x 1 dose		1 x 1 dose

Multiple blood sampling for PK analysis was performed from predose to 168 hr postdose. The data were analyzed using standard noncompartmental methods and compartmental methods (1-compartment model, first-order absorption, first-order elimination, pooled analysis using WinNonlin and a weighting scheme of $1/C^2_{predicted}$). Since 3 doses of Intron A were administered, the area-under-the-curve from time 0 to final quantifiable sample (AUCtf) is presented as the sum of the individual AUCtf after the first, second and third dose.

Results

Two tables, 1 containing the mean PK parameters and the other containing the results of 1-compartment modeling, are located on page 2. The serum concentration-time curve is located on page 3. The use of single-dose only administration of PEG-IFN and a healthy subject population limits the usefulness of the PEG-IFN PK results. Therefore, the results will only be briefly summarized here:

After a single dose of PEG-IFN:

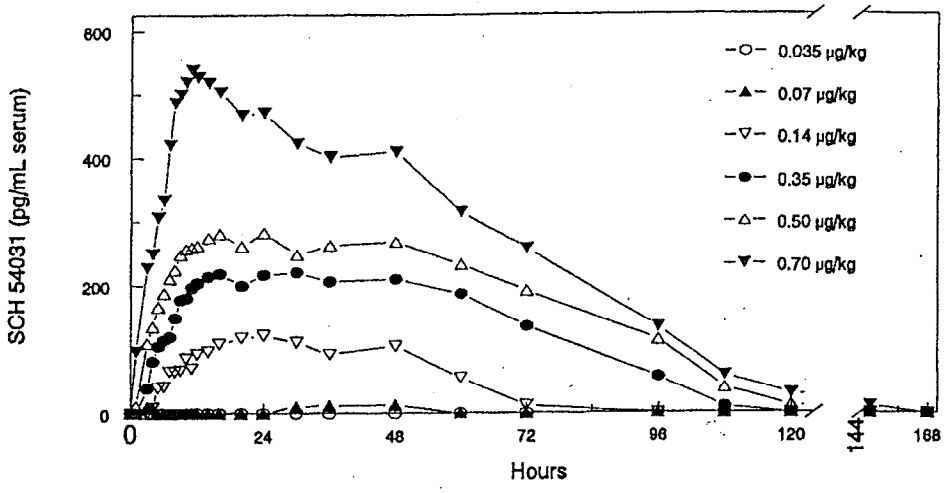
- The maximum serum concentration (Cmax) increases in a less than dose-proportional manner as the dose level increases. Changes in the bioavailability (F) and/or the volume of distribution (V) are potential reasons for the lack of a dose-proportional increase in mean Cmax.
- The mean AUCtf increases in a generally dose-proportional manner with increasing dose level.
- Based on the results of 1-compartment modeling, there is no consistent change in absorption half-life (t1/2α) or mean apparent volume (V/F) as the dose level increases. Alternatively, the apparent clearance (Cl/F) may be increasing slightly, with a corresponding decrease in the elimination half-life (t1/2β), as the dose level increases.

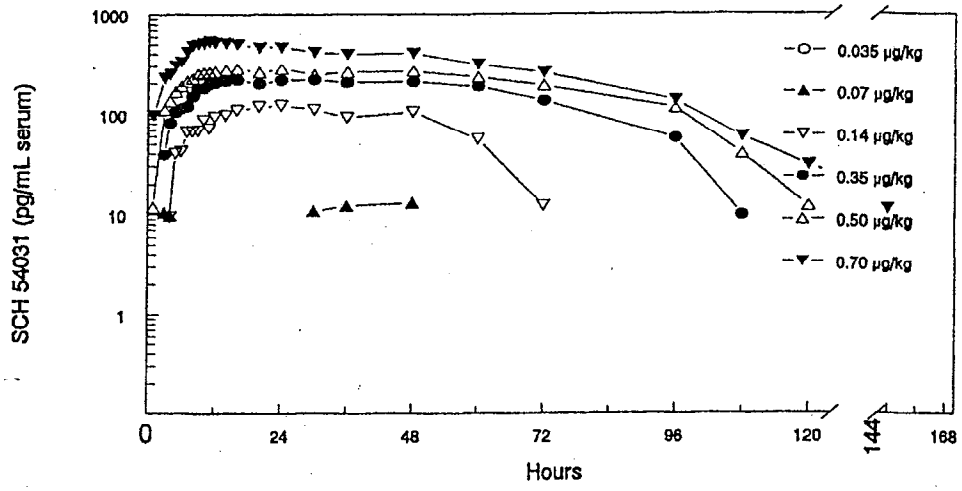
The PK results from this protocol are most useful when comparing a single dose of PEG-IFN to that of Intron A:

- The mean AUCtf for a single dose of 0.5 ug/kg is 13x larger for PEG-IFN than for the FDA-licensed dose of Intron A.
- The duration of measurable serum concentration (tf) of PEG-IFN is 11x greater than for Intron A (0.5 ug/kg PEG-IFN compared to 3 MIU Intron A).
- PEG-IFN has a substantially longer mean Tmax, mean t1/2 β, mean t1/2 α, a smaller mean V/F, and a lower mean Cl/F compared to Intron A.

Conclusions: The differences in the single-dose PK profiles of Intron A and PEG-IFN (a greater AUCtf and tf, a longer Tmax, t1/2 β, and t1/2 α, a smaller V/F, and a lower Cl/F for PEG-IFN) demonstrate the intentional result of pegylation.

Figure 1 Mean Serum SCH 54031 Concentration-Time Profiles in Healthy Volunteers in Linear-Linear (top) and Log-Linear (bottom) form: EIA Data.





To facilitate comparison, the table on page 11 shows the mean (%CV) serum concentrations and PK parameters during Weeks 1 and 4, respectively, for subjects treated with Intron A. For the 3 MIU TIW Intron A dose group:

- The values for mean Cmax, mean Tmax, mean AUCtf, mean tf, mean t1/2β, and mean Cl/F are significantly smaller compared to those from the PEG-IFN group.
- The mean Cmax and mean AUCtf are twice as large at Week 4 than at Week 1. This corresponds to a 50% decrease in the Cl/F and an almost doubling of the t1/2β. The V was not provided but should be 1427 mL/kg for Week 1 and 1168 mL/kg for Week 4. This change in V is not as clinically significant as the change in Cl/F.

Conclusions: The single-dose PK profile in subjects with hepatitis C is generally similar to the single-dose profile seen in healthy subjects in Protocol I95-010 (see page 1). After 4 weeks of once weekly dose administration, the change in the exposure (AUCtf and Cmax) is greater than dose-proportional for all dose levels, including the proposed dose level of 1.0 ug/kg. During this time, a slight decrease in the Cl/F with a slight increase in the t1/2 β is also seen. Intron A also demonstrates this decrease in Cl/F during repeated dosing. A (saturable) receptor-based elimination mechanism is a likely reason for this decline in Cl/F. Based on a t1/2 β of 33-37 hours for the 1.0 ug/kg dose level, steady state should have been achieved within the first week of dosing. If the Cl/F continues to decrease during repeated dose administration, the time to steady state will be longer. The greater than dose-proportional increase in the AUCtf seen during repeated dosing bears watching.

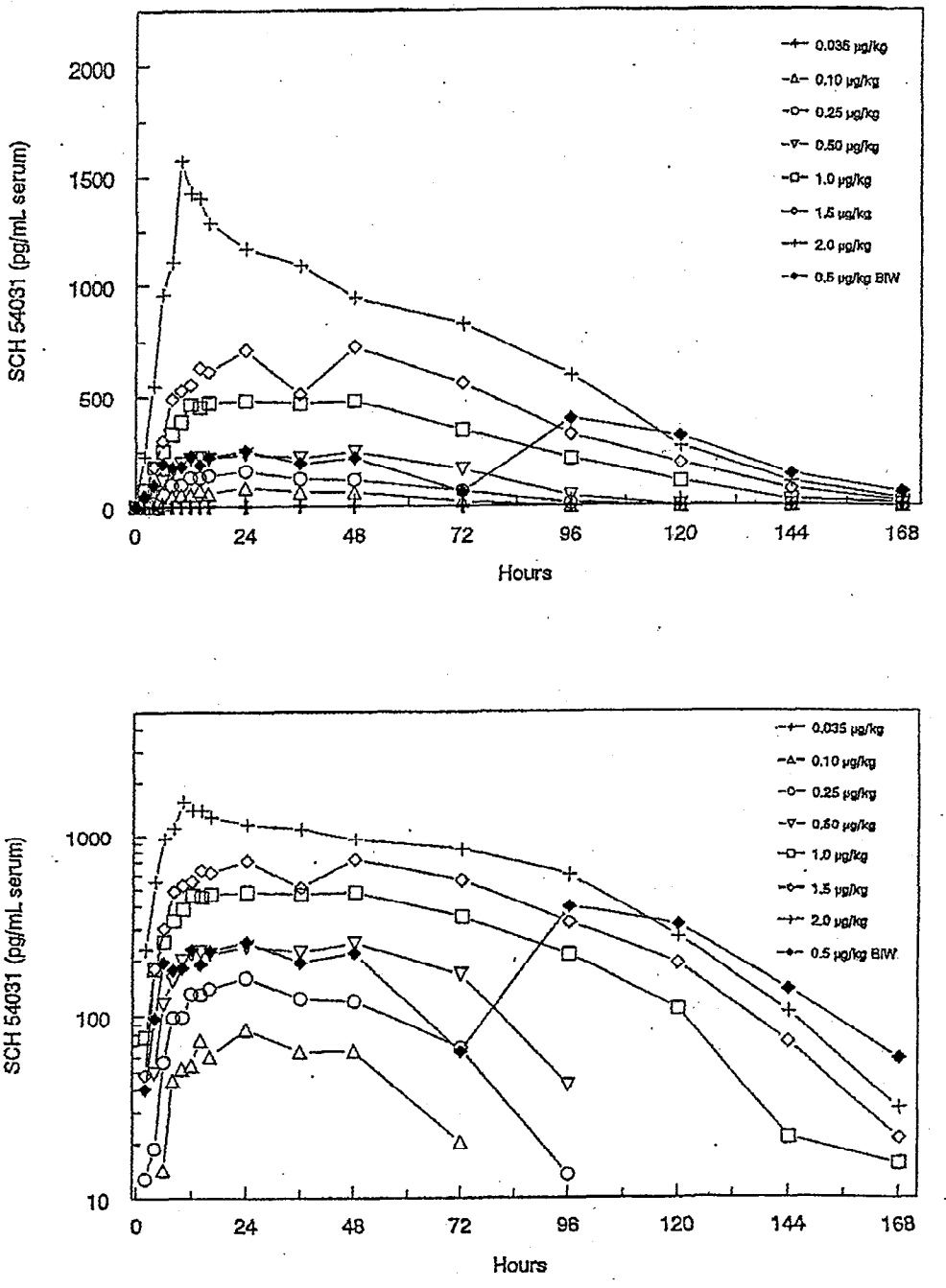


Figure 1. Mean Serum SCH 54031 Concentration-Time Profiles in Patients with Chronic Hepatitis C in Linear-Linear (top) and Log-Linear (bottom) form: Week 1.

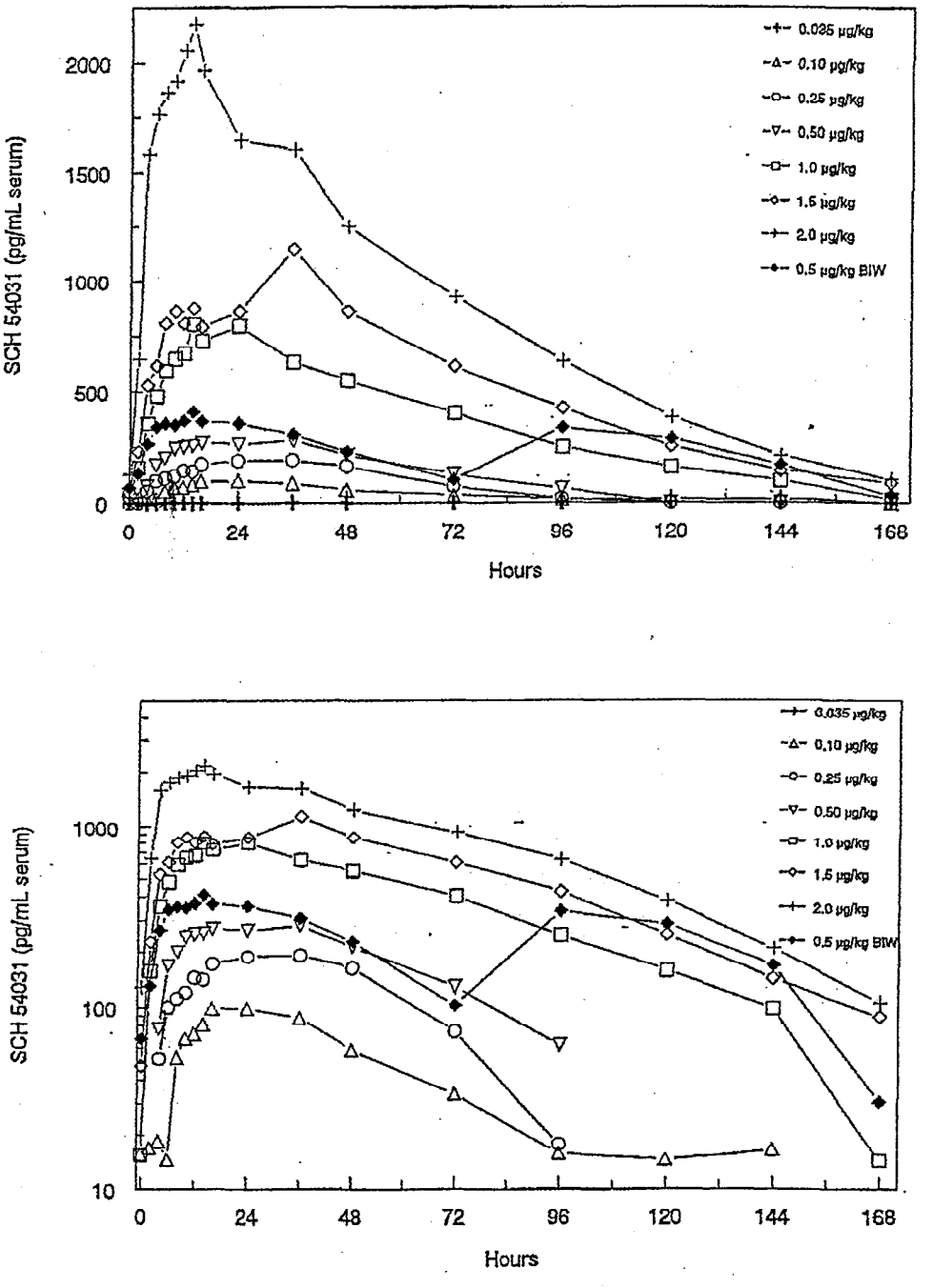


Figure 2. Mean Serum SCH 54031 Concentration-Time Profiles in Patients with Chronic Hepatitis C in Linear-Linear (top) and Log-Linear (bottom) form: Week 4.

Table 3. Mean IFN Serum Concentrations in Patients with Compensated Hepatitis C: Dose - 3 MIU Intron® A TIW.

Hour	Units	Week 1			Week 4		
		Mean	%CV	n	Mean	%CV	n
0		0	NC	16	0.6	NC	16
2		7.0	59	16	14.8	36	16
4		8.7	50	16	20.3	25	16
6		12.3	33	16	22.0	28	16
8		12.9	23	16	20.7	22	16
10		11.4	39	16	17.0	28	16
12		8.3	25	16	13.8	33	16
14		5.3	63	16	10.2	37	16
16		3.7	62	16	9.5	25	14
24		0	NC	16	3.3	87	15
36		0	NC	15	0.4	374	14
48		0	NC	15	0	NC	15
72		0	NC	15	0	NC	15
96		0.4	387	15	1.1	207	15
120		0.3	387	15	0.3	387	15
144		1.0	208	15	3.1	143	15
168		0	NC	15	1.0	209	15
Cmax	IU/mL	14.4	30	16	23.2	21	16
Tmax	hr	8	27	16	6	22	16
AUC(tf)	IU·hr/mL	134	31	16	284	30	16
tf	hr	15	9	16	20	21	16
AUC(I)	IU·hr/mL	182	22	6	373	19	13
t½	hr	4.28	24	6	7.23	25	13
CL/F	mL/kg·hr	231	22	6	112	19	13
Vdarea/F	mL/kg	1400	35	6	1150	25	13

NC - Not appropriate to calculate; division by zero or sample size < 3

Table 8 Mean Trough PEG-Intron and Intron® A Concentrations During Protocols I95-060 and I95-140 (ECL Assay)

	PEG-Intron (pg/mL)								Intron® A (IU/mL)
Dose/ Week	0.035 µg/kg QW [a]	0.1 µg/kg QW	0.25 µg/kg QW	0.5 µg/kg QW	1.0 µg/kg QW	1.5 µg/kg QW	0.5 µg/kg BIW	2.0 µg/kg QW	3 MIU TIW [b]
1	0	0	0	0	15	22	59	31	0
4	0	0	0	0	14	89	30	106	0
8	0[c]	0	0	14	146	195	186	180	2.6[g]
									10.0[k]
16	0[c]	0	235	115	248	281	586	1040	31.6
									122[k]
24	0[c]	35[c]	409[e]	130	598	405	873	940	44.9[h]
									173[k]
28	0[d]	0[f]	74[e]	10[c]	37	0	102[c]	20[c]	16[j]
									61.8[k]

a: PEG-Intron weekly dose, n=6.

b: Intron® A weekly dose, n=16.

c: n=5;

d: n=4;

e: n=3;

f: n=2;

g: n=15;

h: n=14;

j: n=12.

k: Converted to pg/mL using the conversion factor (1 IU: 3.864 pg), based on specific activity.

4. **Protocol C97-040: Single dose PK of PEG-IFN in subjects with various degrees of chronic renal insufficiency**

Methods

This was a Phase 1, open-label, SQ single-dose, 5 parallel-arm study conducted in 6 healthy male and female adults, and 20 male and female adult subjects with stable renal impairment. A single dose of PEG-IFN 1.0 ug/kg SQ was given to all groups except Group 5 (groups noted below). Group 5, the dialysis group, received a first SQ dose of 1.0 ug/kg immediately after dialysis, and 3 weeks later received a second SQ dose of 1.0 ug/kg 12 hr prior to dialysis. The criteria for each group consisted of:

Group	Creatinine Clearance (mL/min/1.73 m^2)
1	≥80
2	50-79
3	30-49
4	10-29
5	<15

Multiple blood sampling for PK analysis was performed from predose to 168 hr postdose. The data were analyzed using standard noncompartmental methods. The relationship between creatinine clearance (CrCl) and Cl/F of PEG-IFN was assessed by regression analysis.

Results

Two tables, the first one containing the mean PK parameters for Groups 1 through 4 and the second table containing the mean PK parameters for Group 5, can be found on page 17. The serum concentration-time curve for all 5 groups is located on page 18 while the graphs on page 19 show the serum concentration-time curves for just Group 5.

- The PK results for Groups 1 through 4 show:
  - There is a steady increase in mean Cmax, mean AUCtf, and mean t1/2 β from Groups 1 to 4.
  - A significant decrease in mean Cl/F occurs from Group 2 to 3 (i.e., when the CrCl drops below 50 mL/min).
  - A noticeable decrease in mean V/F occurs from Group 1 to 2.
- The PK results for Group 5 show:
  - Mean Cl/F is the same between the 2 subsets (Period 1/postdialysis and Period 2/predialysis).
  - Mean t1/2 β and mean V/F are larger in the predialysis subset.
  - Mean Cmax and mean AUCtf are greater in the postdialysis subset. Given the identical Cl/F between the 2 subsets, the greater mean exposure is most likely due to the smaller V/F.
  - In the predialysis subset, a temporary dip in the serum concentration is seen during the dialysis procedure. The sponsor notes that a difference in venous and arterial PEG-IFN concentration was not seen during dialysis. This suggests that the temporary dip in serum concentration was not due to enhanced PEG-IFN elimination but perhaps due to the fluid shifts associated with dialysis.
- A comparison of the PK profiles for Groups 1-4 and Group 5 shows:
  - The mean Cl/F, mean t1/2β, mean V/F, mean Cmax, and mean AUCtf for Group 5 is similar to that for Group 4.
  - The mean Tmax is longer in Group 5 compared to Groups 1-4.

Conclusions: A progressively decreasing creatinine clearance is associated with a progressively increasing exposure to PEG-IFN. This is not surprising since the average molecular weight of PEG-IFN (32 kD) suggests that glomerular filtration, with subsequent reuptake and catabolism by the nephric tubules, is the most likely route of elimination. The relationship between decreasing creatinine clearance and decreasing PEG-IFN apparent clearance proceeds in a stepwise manner. A significant decline in the apparent clearance occurs when the creatinine

Table 5 Mean Pharmacokinetic Parameters of PEG Intron Following a Single 1.0 µg/kg Subcutaneous Dose in Study No. C97-040.

Parameter[a]	Group I[a] (CLcr:>80 mL/min		Group II[b] (CLcr:50-79 mL/min)		Group III[c] (CLcr:30-49 mL/min)		Group IV[a] (CLcr:10-29 mL/min)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
Cmax[d]	591	30	675	--	932	38	1059	36
Tmax[d]	28.0	35	30.0	--	31.2	34	28.0	22
AUC(tf)[d]	51251	31	64379	--	86713	39	97195	32
AUC(I)[d]	56413	36	71806	--	99905	42	116972	36
T1/2[d]	40.1	18	45.1	--	48.1	32	55.6	24
CL/F[d]	26.4	35	25.9	--	16.8	28	14.3	32
CLcr[d]	105	11	63.5	--	38.6	17	21.5	26
Vd/F[d]	87.9	27	65.8	--	66.6	27	66.6	26

a: n=6;
b: n=2;
c: n=5;
d: Unit: Cmax-pg/mL; Tmax-hr; AUC-pg·hr/mL; t1/2-hr, CL/F and CLcr-mL/min; VD/F-L.

Table 6 Mean PEG-Intron Pharmacokinetic Parameters: Effects of Hemodialysis.

Parameters	Group V (Period 1)[a]		Group V (Period 2)[b]	
	Mean	%CV	Mean	%CV
Cmax[c]	1136	33	923	27
Tmax[c]	38.4	26	38.8	57
AUC(tf)[c]	102802	21	96281	19
T1/2[c]	51.9	35	63.7	35
CL/F[c]	12.9	24	12.7	32
Vd/F[c]	60.8	53	72	51

a: n=5 (without Subject 27, see **Section 10.2.**).
b: n=6
c: Unit: Cmax-pg/mL; Tmax-hr; AUC-pg·hr/mL; t1/2-hr, CL/F-mL/min; Vd/F-L.

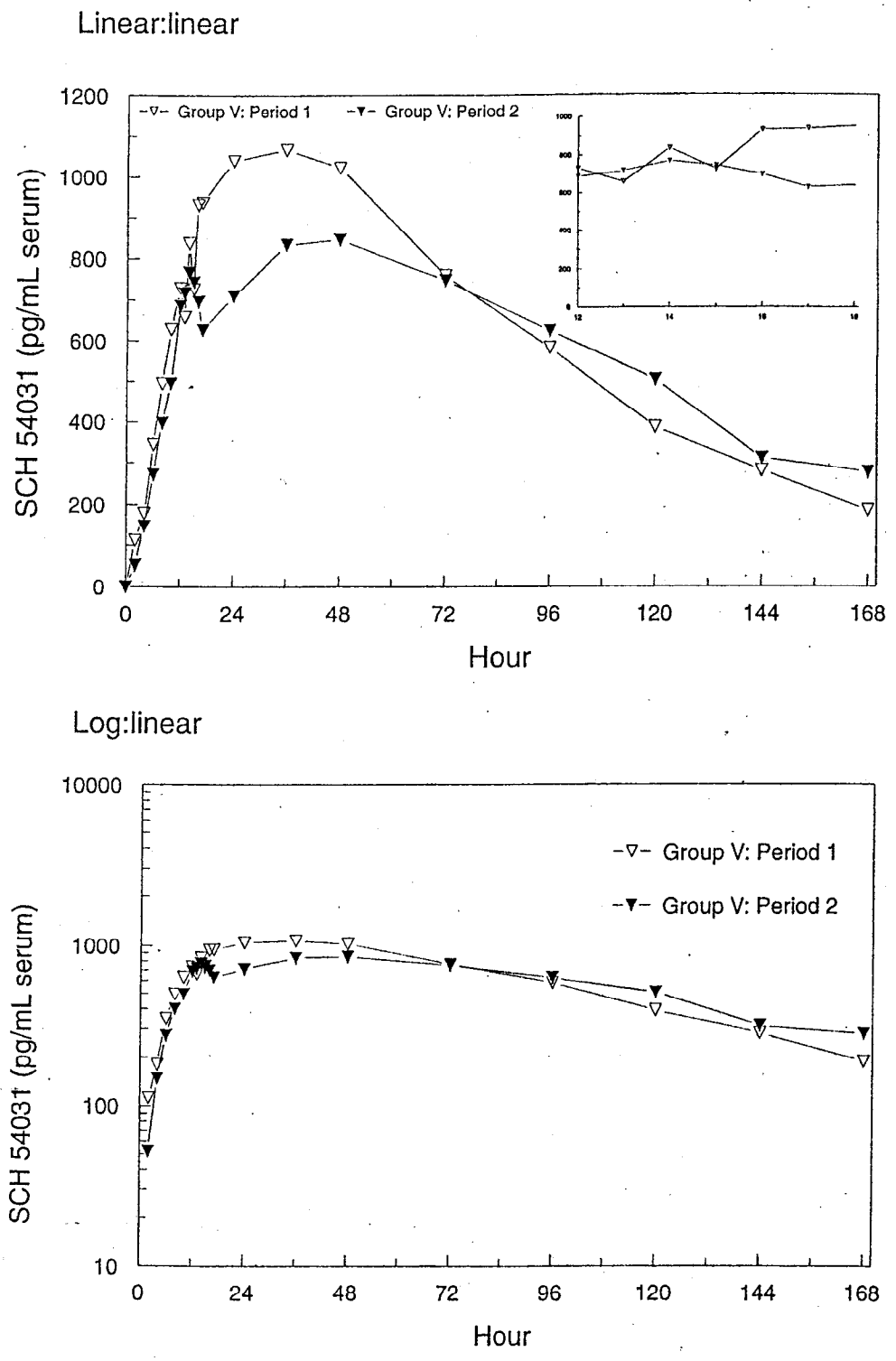


Figure 3 Mean Serum (Venous) PEG-Intron Concentration-Time Profiles (Inset During Dialysis) Following Single Subcutaneous Dose of 1 µg/kg in Periods 1 and 2 to Subjects in Group V

Table 3 Mean Pharmacokinetic Parameters of PEG Intron Following a Single 1.0 µg/kg Subcutaneous Dose in Young and Elderly Subjects (Study No. C97-058).

	Group I (20-45 yr)		Group II (65-69 yr)		Group III (70-74 yr)		Group IV (75-80 yr)	
Parameter[a]	Mean[b]	%CV	Mean[b]	%CV	Mean[b]	%CV	Mean[c]	%CV
Cmax	1044	34	959	37	846	39	1134	42
Tmax	13.7	41	23.3	56	21.3	41	16.0	31
AUC(tf)	65830	48	70339	31	63160	32	60266	34
t1/2	35.8	15	42.5	21	46.9	19	40.5[d]	20
CL/F	20.4	26	16.8	28	19.7	34	17.0[d]	13
Vd/F	61.3	21	61.5	34	80.6	41	60.2[d]	28

a: Unit: Cmax-pg/mL; AUC-pg·hr/mL; Tmax and tf-hr; CL/F: mL/min; CLcr: mL/min; Vd/F: L.

b: n=6.

c: n=5; Subject 21's data excluded as outliers. Mean values including subject 21's data were Cmax: 1492 pg/mL, AUC(tf): 104879 pg·hr/mL; t1/2: 44.4 hr; CL/F=14.4 mL/min; Vd/F: 52.1 L.

d: Could not be determined for Subject 24.

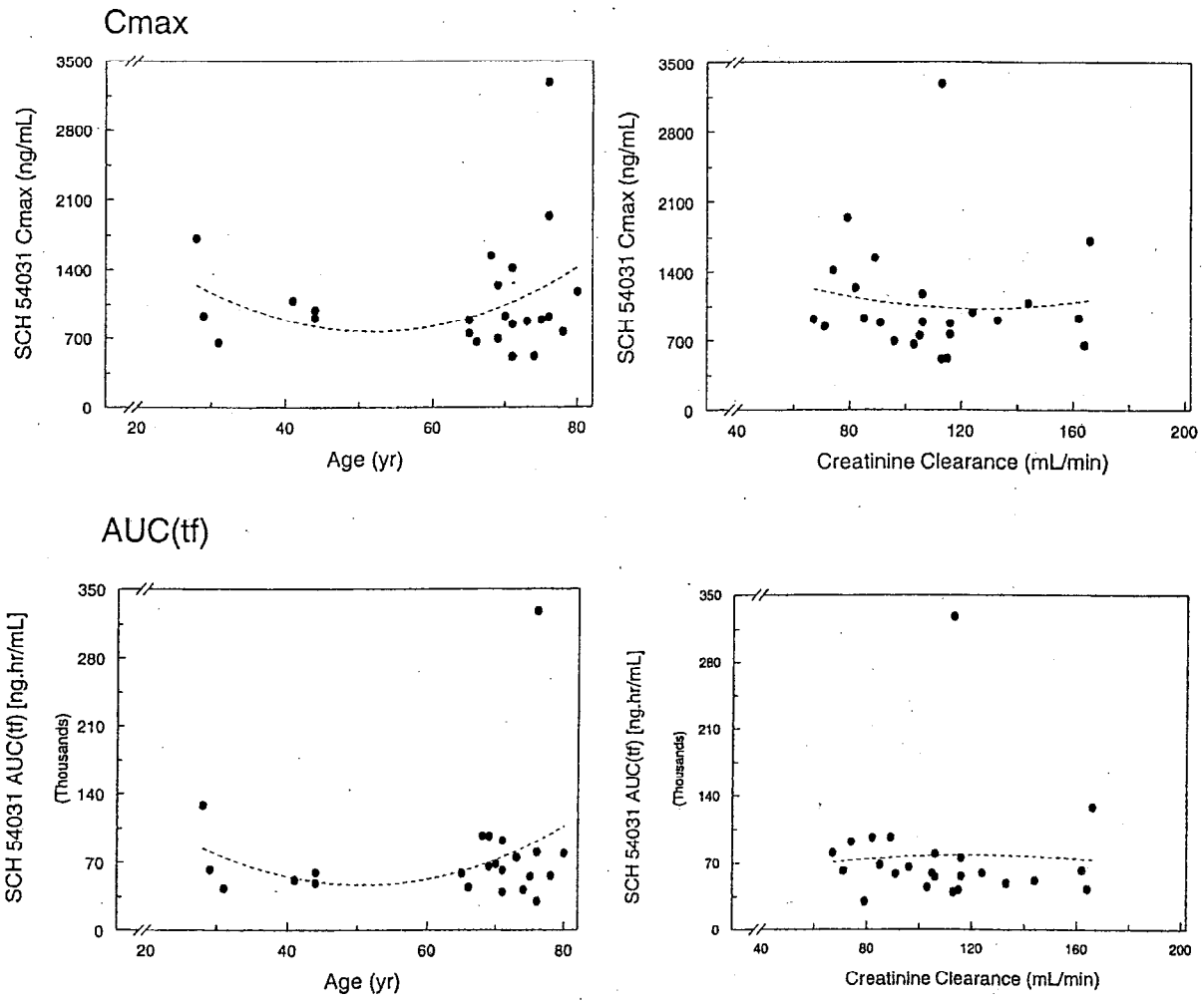


Figure 2 Relationship Between Cmax and AUC(tf), and Covariates (with Smoothing Line).

Conclusions: The medical research literature contains many references to the ability of viral infections, including hepatitis C virus, to decrease the activity of the mixed function oxidase system via an interferons-based mechanism (a decrease in mRNA and P450 synthesis have been documented). Alternatively, it has been reported that CYP2D6 and 2A6 activity can be inhibited by chronic hepatitis C-induced autoantibodies. The literature also notes the possibility that interferons may inhibit 1A2 activity.

Based on the results from this single dose study in healthy men, PEG-IFN does not alter the metabolic ability of CYP1A2, 2C8/9, 2D6, hepatic 3A4 or NAT. A change in CYP2C19 activity was not assessed; the study report did not address this. The usefulness of the above results to the treatment of patients with varying degrees of liver dysfunction due to chronic hepatitis C infection is minimal. On the other hand, the practicality of conducting this protocol in the hepatitis C patient population is doubtful.

Table 1 Mean Plasma Concentrations (pg/mL) and Pharmacokinetic Parameters of SCH 54031 in Study I97-078-01 Following the Administration of 1.0 µg/kg PEG-Intron Subcutaneously

Time (hr)	Unit[a]	Mean	%CV	n
0		0	0	12
2		153	60	12
4		208	49	12
10		406	43	12
12		551	36	12
16		543	38	12
20		557	34	12
24		612	39	12
28		587	29	12
36		594	35	12
48		607	37	12
60		594	42	12
84		471	35	12
108		296	39	12
132		193	47	12
156		104	77	12
Cmax	pg/mL	739	29	12
Tmax	hr	31	61	12
AUC(tf)	pg·hr/mL	62713	34	12
AUC(I)	pg·hr/mL	70359	37	12
t½	hr	37.67	29	12
K	1/hr	0.019	29	12
Vd/F	mL/kg	856	51	12
CL/F	mL/hr/kg	16.24	41	12

a: pg/mL

7. **Protocol I96-403: Safety and tolerability of combined ribavirin and PEG-IFN α-2b in subjects with chronic hepatitis C**

Methods

This was a Phase 1, randomized, open-label, active-controlled, rising multiple-dose, 8 parallel-arm study conducted in 72 male and female adults with chronic hepatitis C but no cirrhosis (n= 9/group; 3 PEG-IFN alone: 6 PEG-IFN and ribavirin). Treatment was administered for 24 weeks. Dose groups:

Group	PEG-IFN Dose (ug/kg/wk)	OR	PEG-IFN (ug/kg/wk) // ribavirin (mg/day)		
1	0.35		0.35	//	600
2	0.7		0.7	//	600
3	0.7		0.7	//	1000-1200
4	1.4		1.4	//	600
5	0.35		0.35	//	800
6	0.7		0.7	//	800
7	1.4		1.4	//	800
8	1.4		1.4	//	1000-1200

Multiple blood sampling for PEG-IFN PK analysis was performed from predose to 168 hr postdose during weeks 1 and 4. Trough and 24 hr postdose sampling for PK was performed during weeks 8 and 12.

Multiple sampling for ribavirin PK analysis was performed at predose and periodically for 12 hr postdose during weeks 1 and 4. Trough ribavirin levels were collected during weeks 12 and 24. A validated HPLC-MS/MS method with LOQ= 50 ng/mL was used to determine the ribavirin serum concentration.

The data were analyzed using standard noncompartmental methods. AUC and Cmax values for PEG-IFN were dose-normalized (to 0.35 mg/kg). The accumulation factor was analyzed using ANOVA, extracting the effect of ribavirin on PEG-IFN. A factorial ANOVA model was also used to analyze the accumulation factor and dose-adjusted (to 0.35 mg/kg) log-transformed AUC and Cmax values. The effects due to dose (of PEG-IFN, and ribavirin) and the interactions were examined.

Results

A summary table with the mean PK parameters for PEG-IFN during weeks 1 and 4 is presented on page 31. The data from 3 subjects, deemed by the sponsor to be statistical outliers, are excluded from the results: 1 subject in the 0.7 mg/kg PEG-IFN plus 600 mg ribavirin group had poor exposure to PEG-IFN [about 10% of mean AUC(tf)] at Week 4, 1 subject in the 0.7 mg/kg PEG-IFN monotherapy group also had poor exposure to PEG-IFN at weeks 1 and 4 [5 and 10% of mean AUC(tf), respectively], and 1 subject in the 1.4 mg/kg PEG-IFN plus 1000-1200 mg ribavirin group had a high Cmax at Week 4 which was about 7-fold higher than his Week 1 Cmax and 4-fold higher than Week 4 mean Cmax of that treatment group. A quick review of the PK profile and demographic attributes of each of these 3 subjects did not reveal an obvious reason for the discrepancies.

- Exclusion of the data from these 3 subjects significantly improves the %CV for the affected dose groups.
- A consistent pattern of change in the PEG-IFN PK profile due to ribavirin is not apparent.
- Minimal accumulation of PEG-IFN is apparent after 4 weeks of treatment with or without ribavirin.
- These PK results are similar to the PK results from the other protocols conducted in subjects with chronic hepatitis C infection without cirrhosis.

The summary table on page 32 shows the PEG-IFN trough and 24 hr postdose data for each dose group (with or without ribavirin) during weeks 8 and 12.

- In the 0.7 and 1.4 ug/kg/week PEG-IFN monotherapy groups, the trough and 24 hr-postdose serum concentrations are similar at weeks 8 and 12, suggesting that steady state has been achieved. This finding is contrary to the results from Protocol I95-140 (see page 12) where steady state had not been achieved after 24

Table 7 Mean (%CV) Pharmacokinetic Parameters of SCH 54031 at Weeks 1 and 4 after Once Weekly SCH 54031 Subcutaneous Dosing as Monotherapy or with SCH 18908 to Patients with Compensated Hepatitis C without Patients 15, 61 and 88

Treatment Group SCH 54031 with or without SCH 18908 (n)	Parameter[a]								
	Cmax	Tmax	AUC(tf)	AUC(0-168 hr)	DN[b]-Cmax	DN[b]-AUC(tf)	t½	R	CL/F·kg
	Week 1								
0.35 µg/kg Monotherapy (6)	242 (27)	20.3 (48)	17842 (41)	18602 (38)	242 (27)	17842 (41)	63.8 (34)	---	---
0.35 µg/kg Monotherapy (6)	301 (42)	30.3 (40)	17187 (17)	18229 (17)	301 (42)	17187 (17)	54.8 (34)	---	---
0.35 µg/kg Monotherapy (6)	209 (24)	24.0 (64)	13784 (32)	14692 (30)	209 (24)	13784 (32)	69.4 (47)	---	---
0.7 µg/kg Monotherapy (8)[c]	390 (36)	32 (63)	32230 (48)	32944 (46)	195 (35)	16115 (48)	49.6 (29)	---	---
0.7 µg/kg and 600 mg (5)[d]	373 (30)	28.4 (89)	28398 (31)	29082 (31)	186 (30)	14199 (31)	46.0 (7)	---	---
0.7 µg/kg and 800 mg (6)	571 (32)	23.0 (66)	36241 (50)	36937 (49)	286 (32)	18121 (50)	35.4 (27)	---	---
0.7 µg/kg and 1000-1200 mg (6)	289 (26)	28.3 (32)	23491 (33)	24311 (30)	144 (26)	11745 (33)	71.5 (84)	---	---
1.4 µg/kg Monotherapy (9)	818 (24)	24.7 (46)	63842 (26)	64411 (26)	205 (24)	15960 (26)	41.2 (18)	---	---
1.4 µg/kg and 600 mg (6)	905 (23)	34.0 (65)	74668 (17)	75124 (16)	226 (23)	18667 (17)	54.4 (87)	---	---
1.4 µg/kg and 800 mg (6)	679 (31)	15.0 (11)	48273 (22)	49149 (21)	170 (31)	12068 (22)	36.1 (32)	---	---
1.4 µg/kg and 1000-1200 mg (5)[e]	655 (36)	34.4 (33)	47449 (24)	48431 (23)	164 (36)	11862 (24)	30.8 (21)	---	---
	Week 4								
0.35 µg/kg Monotherapy (6)	314 (56)	28.3 (32)	20110 (32)	20788 (30)	314 (56)	20110 (32)	52.9 (35)	1.19 (26)	18.3 (33)
0.35 µg/kg and 600 mg (6)	260 (50)	24.3 (42)	15027 (24)	15937 (22)	260 (50)	15027 (24)	48.2 (36)	0.889 (24)	22.9 (24)
0.35 µg/kg and 800 mg (6)	224 (23)	26.7 (29)	14294 (35)	15074 (32)	224 (23)	14294 (35)	44.5 (34)	1.02 (11)	26.1 (43)
0.7 µg/kg Monotherapy (8)[c]	358 (56)	21.8 (59)	24075 (51)	24879 (50)	179 (55)	12038 (51)	49.2 (48)	0.866 (59)	34.5 (44)
0.7 µg/kg and 600 mg (5)[d]	218 (32)	24.0 (0)	16479 (27)	17304 (26)	109 (32)	8239 (27)	82.2 (68)	0.714 (43)	43.1 (33)
0.7 µg/kg and 800 mg (6)	609 (47)	18.3 (54)	38395 (40)	39337 (39)	304 (47)	19197 (40)	38.0 (29)	1.19 (41)	20.2 (38)
0.7 µg/kg and 1000-1200 mg (6)	264 (33)	30.0 (33)	22620 (54)	23166 (51)	132 (33)	11310 (54)	62.1 (55)	0.932 (25)	35.2 (35)
1.4 µg/kg Monotherapy (9)	874 (33)	29.3 (45)	72057 (26)	72311 (26)	219 (33)	18014 (26)	42.5 (24)	1.17 (20)	20.6 (28)
1.4 µg/kg and 600 mg (6)	1097 (23)	26.7 (58)	91563 (19)	91733 (19)	274 (23)	22891 (19)	44.1 (37)	1.22 (8)	15.8 (21)
1.4 µg/kg and 800 mg (6)	805 (26)	28.7 (30)	58406 (24)	59084 (24)	201 (26)	14602 (24)	35.7 (14)	1.20 (10)	24.8 (22)
1.4 µg/kg and 1000-1200 mg (5)[e]	823 (36)	27.2 (32)	64472 (17)	64594 (17)	206 (36)	16188 (17)	38.1 (28)	1.37 (20)	22.3 (21)

Table 9 Mean Plasma Concentration-Time Data and Pharmacokinetic Parameters of SCH 18908 at Weeks 1 and 4 after Twice Daily Oral Dosing with SCH 54031 to Patients with Compensated Hepatitis C

	SCH 18908 (ng/mL)					
	600 mg[a]		800 mg[a]		1000-1200 mg[a,b]	
Hour	Mean	%CV	Mean	%CV	Mean	%CV
	Week 1					
0	0	---	0	---	0	0
0.5	394	95	346	68	452	41
1	623	69	674	43	982	39
1.5	637	59	751	42	926	28
2	627	58	648	42	843	46
3	481	59	504	46	583	30
4	378	54	399	39	534	34
6	351	50	323	35	425	45
8	262	50	276	38	358	33
10	235	56	251	37	288	37
12	229	62	206	38	254	31
Cmax[c]	741	56	799	40	1101	38
Tmax[c]	1.44	37	1.50	34	1.46	31
AUC(0-12 hr)[c]	4271	53	4381	36	5592	29
DN[d]-Cmax	741	56	600	40	650	38
DN[d]-AUC(0-12 hr)	4271	53	3286	36	3281	26
tf[c]	12.0	0	12.0	0	12.0	0
	Week 4					
0	1068	28	1379	33	1876	31
0.5	1480	34	1796	32	2412	25
1	1636	33	1981	32	2563	23
1.5	1632	33	2025	33	2510	22
2	1614	31	1998	32	2349	22
3	1567	29	1914	35	2325	24
4	1450	28	1828	29	2114	17
6	1364	25	1683	37	2036	23
8	1216	28	1448	34	1872	20
10	1206	32	1526	46	1730	20
12	1104	28	1333	28	1698	21
Cmax[c]	1770	30	2297	33	2750	21
Tmax[c]	1.50	58	2.03	117	1.00	80
AUC(0-12 hr)[c]	16240	28	19040	32	24359	19
DN[d]-Cmax	1770	30	1723	33	1624	21
DN[d]-AUC(0-12 hr)	16240	28	14280	32	14359	18

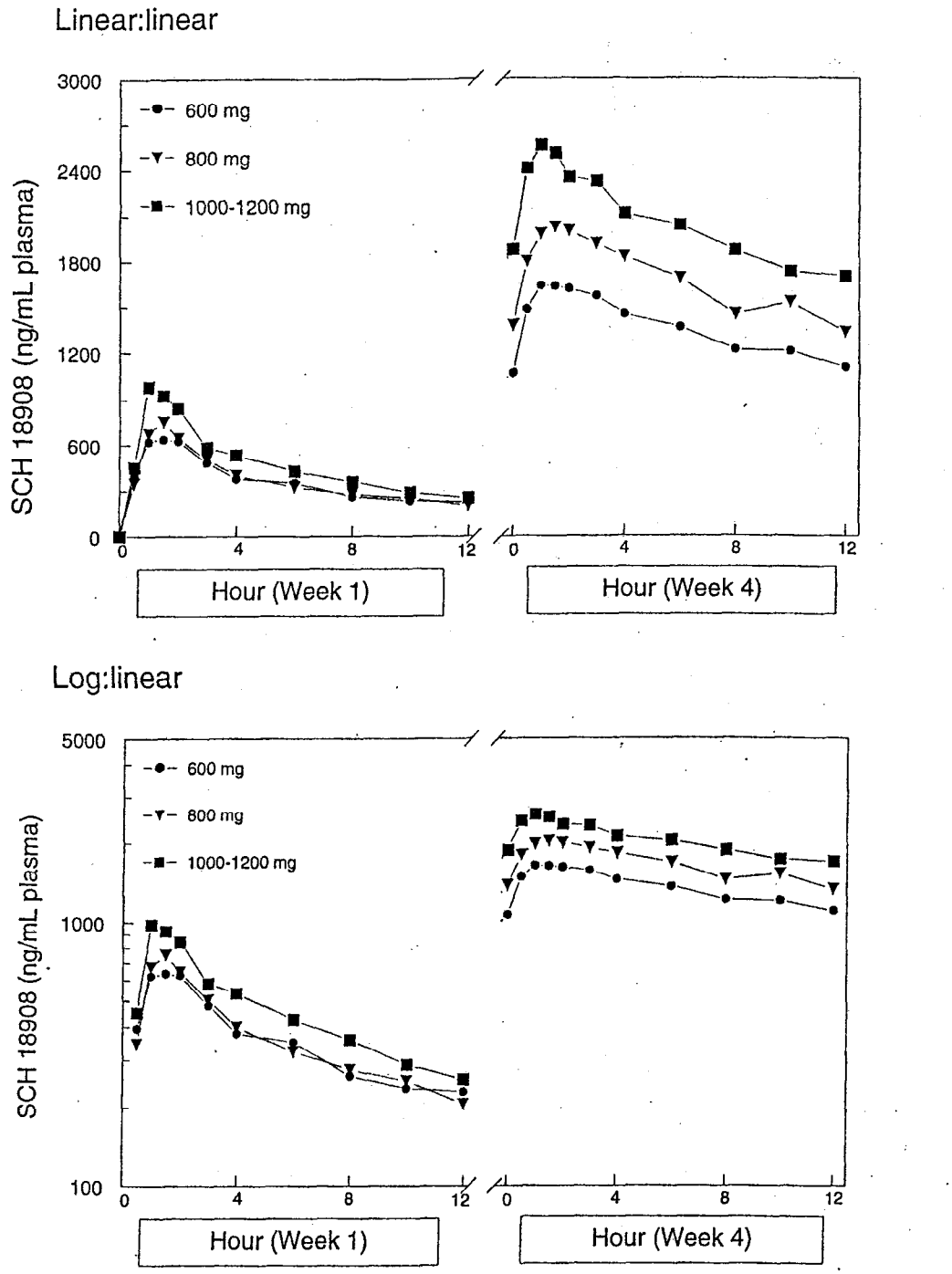


Figure 10 Mean Plasma Ribavirin Concentration-Time Profiles After 600, 800 and 1000-1200 mg (Divided Daily Doses) Ribavirin Twice Daily Oral Dosing to Patients with Compensated Hepatitis C (Protocol I96-403)

Table 4 Mean Trough Serum PEG Intron Concentrations Between Weeks 4 and 48 (All Patients; Protocol C/I97-010)

Dose Group	Treatment Weeks				
	4	12	24	36	48
0.5 µg/kg	45±71 (143) (0,626)	70±106 (109) (0,731)	133±275 (104) (0,1788)	162±277 (96) (0,1471)	152±256 (73) (0,1479)
1.0 µg/kg	105±91 (121) (0,638)	148±129 (109) (0,675)	248±250 (97) (0,1236)	304±381 (87) (0,1832)	273±389 (76) (0,2960)
1.5 µg/kg	201±203 (130) (0,1894)	234±219 (114) (0,1942)	379±450 (106) (0,3130)	425±515 (81) (0,3670)	434±444 (70) (0,2718)

Data presented as mean ± SD (n) (range). Units = pg/mL.

Table 6 Mean Trough Serum PEG Intron Concentrations Between Weeks 4 and 48 (All Patients; Protocol C/I97-010)

Gender	Dose Group	Treatment Weeks				
		4	12	24	36	48
Female	0.5µg/kg	48±88 (64) (0,626)	56±78 (47) (0,314)	69±128 (44) (0,671)	118±198 (39) (0,1139)	166±264 (30) (0,1336)
	1.0 µg/kg	93±77 (50) (0,416)	148±121 (47) (0,675)	241±227 (36) (0,1156)	332±408 (42) (0,1832)	374±599 (28) (0,2960)
	1.5 µg/kg	177±137 (56) (0,672)	211±142 (46) (0,726)	395±443 (40) (0,1603)	395±424 (33) (0,2135)	378±291 (30) (59,1154)
Male	0.5 µg/kg	43±55 (79) (0,196)	80±122 (62) (0,731)	180±339 (60) (0,1788)	192±319 (57) (0,1471)	142±253 (43) (0,1479)
	1.0 µg/kg	113±99 (71) (0,638)	148±135 (62) (0,667)	251±264 (61) (0,1236)	278±357 (45) (0,1616)	214±162 (48) (0,746)
	1.5 µg/kg	219±241 (74) (0,1894)	249±258 (68) (0,1942)	370±457 (66) (0,3130)	445±574 (48) (0,3670)	477±531 (40) (0,2718)

Data presented as mean ± SD (n) (range). Units = pg/mL.

Conclusions:

- Compared to Intron A, the single dose PK profile of PEG-IFN in subjects with hepatitis C exhibits a greater AUCtf and tf, a longer Tmax, t1/2 β , and t1/2 α, a smaller V/F, and a lower Cl/F. After 4 weeks of PEG-Intron administration with 1.0 ug/kg/week, subjects with hepatitis C had ~200-fold greater exposure by area-under-the curve[tf], ~7-fold increase in duration of measurable serum levels, ~5-fold increase in elimination half-life, and ~7-fold decrease in apparent clearance. These findings demonstrate the intentional result of pegylation.

- After 4 weeks of once weekly PEG-IFN dose administration, a greater than dose-proportional change in the exposure (AUCtf and Cmax) is evident for the dose range 0.1 to 2.0 ug/kg/week, including the proposed dose level of 1.0 ug/kg/week. A slight decrease in the Cl/F with a slight increase in the t1/2 β occurred during this time.

  Intron A also demonstrates this decrease in Cl/F during repeated dosing. A (saturable) receptor-based elimination mechanism is a likely reason for the decline in Cl/F.

- After 48 weeks of PEG-IFN monotherapy with the proposed dose regimen of 1.0 ug/kg/week in the proposed patient population, dose proportionality in the PEG-IFN trough levels is evident, a 2.2 to 3.4-fold increase in the mean trough is seen. A gender-related change in trough levels is not apparent. Steady state, as determined by trough levels, was achieved by week 36 of dose administration for the proposed dose regimen with an accumulation ratio of 2.90.

- A progressively decreasing creatinine clearance is associated with a progressively increasing exposure to PEG-IFN. This finding is consistent with a predominantly renal-based clearance for PEG-IFN. With a molecular weight of 32 kD, glomerular filtration and subsequent reuptake and catabolism by the nephric tubules, is the most likely route of elimination. The relationship between decreasing creatinine clearance and decreasing PEG-IFN apparent clearance proceeds in a stepwise manner. A significant decline in the apparent clearance occurs when the creatinine clearance is below 50 mL/min. The differences in the safety database, if any, for subjects with a creatinine clearance of <50 mL/min should be used as a guide to determine if a lower dose is necessary.

  The changes in PEG-IFN exposure seen pre- versus post-dialysis are most likely secondary to the fluid shifts associated with the procedure. The apparent clearance is the same before and after dialysis. Minimal difference in PK parameters is seen between the subjects on dialysis and subjects with a creatinine clearance of <50 mL/min.

- Age-related changes in the PK profile were not evident after a single SQ dose of 1.0 ug/kg. However, only adults were studied, the sample size was small and the variation in the data was large.

- Based on the results of a single dose study in healthy men, PEG-IFN does not alter the metabolic ability of CYP1A2, 2C8/9, 2D6, hepatic 3A4 or NAT. A change in CYP2C19 activity was not assessed. The usefulness of these results to the treatment of patients with varying degrees of liver dysfunction due to chronic hepatitis C infection is minimal. However, the practicality of conducting this protocol in the hepatitis C patient population is doubtful.

  The medical research literature contains many references to the ability of viral infections, including hepatitis C virus, to decrease the activity of the mixed function oxidase system via an interferons-based mechanism (a decrease in mRNA and P450 synthesis have been documented). Alternatively, it has been reported that CYP2D6 and 2A6 activity can be inhibited by chronic hepatitis C-induced autoantibodies. The literature also notes the possibility that interferons may inhibit 1A2 activity.

- Twelve weeks of PEG-IFN/ribavirin combination therapy resulted in consistently lower PEG-IFN trough levels compared to PEG-IFN monotherapy. The difference was greatest at week 8 (2-fold lower) for the 0.7 and 1.4 ugkg/week dose groups compared to the difference at week 12 (less than 1-times lower). Data beyond week 12 were not available. Differences in the clearance and/or bioavailability are the most likely reason. A significant change in the ribavirin PK profile due to concurrent PEG-IFN therapy was not evident.